RESPONSE TO THE EXTERNAL PEER-REVIEW AND PUBLIC COMMENTS
Draft Toxicological Review of Benzene (noncancer effects)
(EPA/NCEA-S-0455, September, 1998)

On October 6, 1998, the National Center of Environmental Assessment (NCEA), within the U.S. Environmental Protection Agency's Office of Research and Development, announced in the *Federal Register* (Fed. Reg. 63 (193): 53645-53655, 1998) the availability of a draft document entitled *Toxicological Review of Benzene (noncancer effects)* (EPA/NCEA-S-0455, September, 1998) for a 45-day public review and comment period. The comment period was to close November 24, 1998 but closure was extended to December 31, 1998 in response to a public request.

The *Federal Register* (FR) also announced that the American Institute of Biological Sciences (AIBS), an EPA contractor, would conduct a peer-review workshop on October 28, 1998, to conduct an independent review of the draft document. An expert panel, consisting of five reviewers, was charged by the AIBS to independently critique this document and to prepare a written report that conveys the Panel's opinion on the strengths and weaknesses of the document specifically focusing on:

1. Technical adequacy of the assessment of the long term health effects from exposure to benzene and the identification of key studies that provide the basis for health concern,
2. Establishment of the appropriate no-observed-adverse-effect level/lowest-observed adverse-effect level (NOAEL/LOAEL),
3. The reasonableness and rationale for recommending the RfD/RfC, and the assumptions and uncertainty factors used in its calculations, and the
4. Assessment of whether the document reflects EPA's published risk assessment guidelines for noncancer effects and for the derivation of RfD and RfC.

The summary report of the External Peer Review Panel entitled *Peer Review of the U. S. Environmental Protection Agency Draft Document* was made available to the public. The views of the panel with respect to the EPA questions is the basis of the summary report.

Public comments were received from two groups during the public review and comment period. Their names and the dates of comments are as follows:

American Petroleum Institute, 12/30/98
Consultants in Toxicology, Risk Assessment and Product Safety, 1/8/99.

The comments from these groups addressed the following general categories: The selection of biological endpoints, the particular choice of key studies, the application of uncertainty factors in the calculation of the risk from exposure to benzene, the nature of the peer-review meeting, the scientific quality of the draft toxicological review and the relationship of the draft toxicological review to a previous document on benzene, *"Carcinogenic Effects of Benzene: An Update",* (EPA/600/P-97/001F; April, 1998).

The remainder of this report summarizes and responds to the comments received from the expert panel and from the public during the review and comment period.

EXTERNAL PEER REVIEW PANEL

1. **COMMENT:** The document, its format and general content do not adequately fulfill the intent of the Agency to characterize and select the most "critical" noncancer health effects from exposure to benzene and derivation of RfC and RfD. The format organizes data on the basis of route of administration but does not provide for integration of data taken from studies using different routes.

RESPONSE: The format and intent of the Toxicological Review of Benzene (Noncancer effects) is a standard format used for the several scientific background documents routinely developed in support of the IRIS summaries. The Agency agrees with the Peer Review Panel's comments on the lack of integration of data throughout the document. In the revised document the Agency has provided a more thorough evaluation and integration of the database including discussion and summary for each topic throughout the document in response to the Peer Review Panel's comments. Specific to the relative contributions of different routes, the Agency has summarized information on species, route and dose rate differences in Section 3.3 under metabolism.

2. **COMMENT:** The choice of principal studies for calculating RfD and RfC are questionable as are the uncertainty factors (UF) used. The authors failed to establish a dose-response relationship with respect to increasing exposure to benzene and changes in blood hematology and the assessment of exposure in the subjects examined in the study.

RESPONSE: The Agency reexamined the choice of principal studies and developed a better scientific rationale based on several epidemiological and experimental animal studies published in the peer-reviewed literature and modified its use of uncertainty factors. The Agency noted concerns of the Peer-Review Panel about the selection of the Rothman et al (1996a) study as well as inadequate discussions of other epidemiologic studies. The Agency reevaluated the relevant epidemiological studies and has included expanded discussions of those studies including LOAELs and NOAELs wherever appropriate. This reevaluation of the pertinent published epidemiological studies and experimental animal data still leads to the conclusion that the Rothman et al (1996a) study is the principal study for derivation of RfD and RfC. That conclusion is supported by several other human and animal experimental studies. The Agency included a detailed discussion of the strengths and weaknesses of the Rothman et al (1996a) study as well as that of other studies mentioned by the Peer Review Panel. An expanded discussion of the attributes of the key studies will be found in section 4.1, 4.2, 5.1, 5.2 as well as a more thorough discussion of uncertainty factors will be found in sections 5.1, 5.2, and section 6.2.

The purpose of the Rothman et al (1996a) study was to show that exposure to benzene affects all the major peripheral blood elements and that hematotoxicity may occur at benzene exposures under 31 ppm. And that the absolute lymphocyte count (ALC) is the most sensitive indicator of benzene-induced hematotoxicity. The approach to evaluating benzene exposure was validated in the overall cohort study by Dosemeci et al (1996), where ALC has been linked to the risk of benzene poisoning (BP). The cutoff point, which was the median exposure level, was based on current exposure only and used personal monitoring data collected 1-2 weeks prior to

blood sample collection. The groups were defined based on exposure patterns, using a standard analytic technique frequently applied in epidemiologic studies, namely the use of the median. The median for the lower exposed group was 13.6 ppm (mean = 14.5 ppm) while the median for the higher exposed group was 91.9 ppm (mean = 109.2 ppm). Both measures are similar.

3. **COMMENT:** One correlation that is consistently missing is the need to relate oral exposure to inhalation exposure.

RESPONSE: The relationship of oral to inhalation and to dermal exposure is extensively discussed and expanded upon in section 3 entitled, "Toxicokinetics Relevant to Assessment" as well as in the earlier IRIS entry entitled, "*Extrapolation of the Benzene Inhalation Unit Risk Estimate to the Oral Route of Exposure* (EPA/NCEA-W-0517, July 1999)".

4. **COMMENT:** The document needs to use primary references rather than secondary references.

RESPONSE: The revised document reflects the use of only primary references. The secondary references such as the Agency for Toxic Substances and Disease Registry (ATSDR) toxicological profile for benzene was used as a resource document only.

5. **COMMENT:** The document has no information on the genetic toxicity of benzene.

RESPONSE: A discussion on genetic toxicity has been expanded in Section 3.3.6, "Mechanism of Toxicity", however, much more detailed documentation will be found in the companion document in IRIS discussing the benzene cancer unit risk entitled, "*Carcinogenic Effects of Benzene: An Update"*, April, 1998, EPA/600/P-97/001F.

6. **COMMENT:** The Agency needs to use more appropriate references to demonstrate an understanding of the mechanism of action of benzene leading to toxicity and other untoward effects.

RESPONSE: A new expanded Section 3.3.6. entitled, "Mechanism of Toxicity" discusses in more explicit detail the mechanisms of action of benzene toxicity.

7. **COMMENT:** A clear and comprehensive section on Synthesis and Evaluation of Major Noncancer Effects and Mode of Action should be added.

RESPONSE: The Agency agrees with the Peer-Review Panel's comment and relevant discussion has been included in Section 4.5, beginning on page 120.

8. **COMMENT:** Indicate whether the unpublished studies that were cited were conducted according to good laboratory practices (GLP) guidelines.

RESPONSE: Since no unpublished data or studies were evaluated for preparing the document, the question of GLP guidelines is not applicable.

9. **COMMENT:** Only published peer-reviewed literature should be used in the final determination of the RfC/RfD levels. Several references were cited that were not published in peer reviewed journals. The fact that these references did not undergo peer review should be clearly stated when these studies are discussed in the document.

RESPONSE: The Agency's revised document only includes review of publications available in the open literature.

10. **COMMENT:** Regarding section 3. entitled, "Toxicokinetics Relevant to Assessments", the peer review panel noted that the EPA failed to provide any discussion, interpretation or ultimate conclusion that could significantly aid in the hazard characterization or the derivation of the RfD and RfC.

RESPONSE: The Agency agrees with the peer review panel and has provided a new section 3.6. that summarizes the interrelationships of the toxicokinetics of benzene and the hazard characterization in the revised document.

11. **COMMENT:** In Section 3.3. entitled "Metabolism", the peer review panel indicated that the toxic effects due to benzene exposure are the result of the net effects based on exposure to several of the metabolites in combination. This concept should be reflected in this section. The EPA should provide summary comments in order to integrate the information on metabolism of benzene and how this information does or does not provide insights as to the mode of action of benzene or if there is a consensus as to the metabolites of benzene responsible for toxicity.

RESPONSE: The agency agrees with the peer panel and has expanded discussion of section 3.3 to facilitate a better understanding of these concepts.

12. **COMMENT:** Section 3.5. "Physiologically Based Pharmacokinetics (PBPK) Modeling" should be changed to include a brief explanation of PBPK modeling and the statement that models are "not sufficiently refined to allow them to predict human metabolism accurately" should be expanded to be more specific regarding the refinements the Agency believes are necessary to make them more accurate. In addition, the compartmental PBPK model developed by Seaton et al (1995) should be included in this section.

RESPONSE: The Agency agrees with the panel and has revised this section accordingly.

13. **COMMENT:** The peer review panel noted that given the uncertainties in the exposure assessment in the Rothman et al study (1996a), it would be of interest to know whether the reassignment of individuals to the other putative exposure group would alter the results, since that appears to have been, at least partly, performed on a subjective basis.

RESPONSE: The assignment of individuals to each exposure group did not have a subjective component. Assignment was based on the geometric mean of 5 days worth of air sampling. The exposure distribution among the 44 workers was bimodal, with only 1 worker having exposure between 31 and 35 ppm benzene. If that worker was deleted, and if that worker was assigned to the lower exposed group, if the 3 workers with between 25 and 30 ppm benzene exposure are assigned to the >31 ppm group, or if all workers between 25 and 35 ppm are deleted, the overall trend tests for the ALC are minimally affected according to the authors (Correspondence from Nathaniel Rothman, NCI dated 7/28/99).

14. **COMMENT:** The peer review panel interpreted that only absolute lymphocyte count was significantly different between the control group and subjects exposed to >31 ppm contrary to what Rothman et al (1996a) said in their paper. The Panel suggested that a trend test could be used to evaluate whether a dose-response exists among the various groups.

RESPONSE: Actually, a conservative test for trend using benzene-exposed workers only was employed by Rothman et al. (1996a) in their analysis (a nonparametric test of rank order correlation between benzene air levels and metabolite levels in urine and each hematologic outcome). The p value for the test for linear trend for the ALC, adjusted by linear regression for

age and sex, the matching variables, across the unexposed, lower and higher exposed workers was $p<0.0001$. This was unaffected after adjustment for potential confounders and was done using categories of each of the three exposure groups coded as 1, 2 and 3. The p value for the trend test was identical when the median or mean benzene exposure of each group was used. Further, the trend test using the 8 hr TWA benzene air level (geometric mean of 5 samples) as a continuous measure for each subject (and assuming the exposure received by administrative workers was the same as in the control factory) was also $p<0.0001$. Similarly, trend tests, adjusted for age and sex, for platelets and red blood cells using all subjects were statistically significant according to the authors of the study (correspondence from Nathaniel Rothman, NCI, dated 7/28/99)..

15. **COMMENT:** The peer review panel observed that although a dose-response is not necessary for the determination of a RfC or RfD, the establishment of a dose-response relationship would strengthen the choice of the Rothman et al. (1996a) study as the critical study.

RESPONSE: The Agency agrees with the both observations of the Panel concerning the lack of a need for a dose-response to determine the RfC and RfD and that the presence of one would strenghen the choice of Rothman et al (1996a) as the critical study. However, with regard to the second observation, the presence of a dose-response relationship is already evident. The p values for dose-response among exposed workers is given in the response to items 14. Table 4-3, consisting of the means of the 6 peripheral *dependent* blood parameters analyzed by Rothman et al. (1996a) and arrayed according to 3 *independently* selected exposure categories 0 ppm, <31 ppm and >31 ppm, has been added to the document. In all 6 blood measurements, the mean values at >31 ppm benzene exposure are significantly different from the mean values at 0 ppm exposure. All 6 exhibit monotonic changes indicative of a dose-response relationship. Thus, dose-response relationships are present in every blood measure tested for the data.

16. **COMMENT:** The panel also suggested that based upon two statements from the Rothman et al. (1996a) study, i.e. that the absolute lymphocyte counts derived by two different methods are not the same and that small changes in the ALC are unlikely to have any short term clinical consequences per se, then, at least for the lowest categories under 31 ppm exposure, the effects seen may have limited biological relevance within the context of the development of a reference dose or concentration.

RESPONSE: Rothman et al (1996a) discussed limitations of manual counting as compared to the Coulter Counter. Rothman and colleagues used a Coulter counter to generate a total WBC as well as the % lymphocytes as well as doing a manual count. The machine counts 10,000 cells while the manual count involves counting a standard 100 cells. The hand counts are subject to human scoring error. More accurate counts could be thus be expected from the Coulter counter. The Coulter counting machine actually generated larger and more significant differences in the ALC between the exposure groups than did manual counts. The authors indicated that previous studies that reported ALC and percent lymphocytes based upon manual counts may have underestimated group differences due to nondifferential measurement error.

With respect to the second point, although Rothman et al. (1996a) did not conclude that the effects they observed were due to any particular exposure to benzene under 31 ppm, yet they did conclude that hematotoxicity probably occurs at benzene exposures under 31 ppm, and that ALC is likely to be the most sensitive indicator of benzene exposure under 31 ppm, they point out that in addition to their study, Dosemeci et al (1996) provided additional evidence that

exposure to benzene <31 ppm is associated with an increased risk of hematotoxicity. A 2.2 significantly increased risk of benzene poisoning (BP) among workers exposed to 5-19 ppm benzene was observed compared to workers exposed at <5 ppm in that study. Rothman et al. (1996a) pointed out that a decrease in ALC contributed substantially to the decrease in total WBC observed in the benzene poisoning cases of Dosemeci et al (1996). These and other relevant details are found in section 4.1.2.1. of the revised document under discussions of the Dosemeci et al (1996) study and the Rothman et al (1996a) study.

17. **COMMENT:** The panel requested that more details concerning the weaknesses of the study design of the Rothman et al. (1996a) paper be provided.

RESPONSE: Additional details regarding this issue and others are incorporated in section 4.1.2.1. The information regarding temporal relationships was provided in the Rothman paper. Benzene air samples were collected on 5 separate days during the 1 to 2 week period prior to phlebotomy. The means were similar to the medians and all trend tests were essentially identical. Individual hematology measurements on the subjects were presented for exposed workers only by Rothman et al. (1996a) in their Table V. Data on benzene metabolites were presented in Tables III and V of Rothman et al. (1996a) and have now been added to this section.

18. **COMMENT:** The Panel indicated that the sources of variability in the individual exposures in the Rothman et al (1996a) study should be discussed. The range of ALCs reported in the study are wide compared to the reported benzene exposure measurements. For example, for the group with median exposures of >31 ppm, the lowest lymphocyte count is 0.9 compared with the control's lowest of 1.1. The range of TWA benzene exposures in this >31 ppm group indicates the highest value is 328.5 ppm, a concentration of benzene that would produce extremely severe hematotoxicity in experimental animals.

RESPONSE: A discussion of the sources of individual variability has been added to the document section 4.1.2.1. Although air exposure to benzene may have been overestimated among workers wearing marginally effective respirators, a comparison of urinary phenol levels to the air benzene levels can be made. Urinary phenol is thought to increase in a linear fashion up to 100 ppm benzene. Roughly, 50 ug/mg creatinine is thought to be equivalent to an 8 hr TWA of 10 ppm benzene. For the 19 workers exposed to >31 ppm who had an air and urine sample taken on the same day, the median benzene exposure was 73 ppm and the median urine phenol level was 351 ug/mg creatinine, about what one would predict. This is a test of the validity of the benzene air sampling effort. Dosemeci et al., 1996 estimated that only about 5% of more than one thousand workers who were exposed to 100 ppm or higher of benzene in their factories were diagnosed with benzene poisoning. It is not known if severe hematotoxicity occurred to that one individual in 19 who was reported to have a TWA of 328.5 ppm. It is not always possible to obtain a perfect correlation between a surrogate measure of exposure and its effect.

19. **COMMENT:** The panel indicates that the NTP (1986) studies of benzene exposure in rats and mice were the most important studies ever performed on benzene but the draft document does not use them to calculate the RfD because a NOAEL was not identified. Furthermore, the Panel noted that the Hsieh et al. (1988a,b) data offered a LOAEL that is less than other studies. Are these objections sufficient to preclude use of the NTP (1986) data.

RESPONSE: The Agency agrees with the Panel. The NTP (1986) data is now used as a co-

principal study in the derivation of an RfD along with the Rothman et al (1996a) human study as well as for calculation of benchmark dose. The Hsieh et al (1988a,b) is now considered a supporting study to the NTP (1986) study and was rejected for derivation of RfD/RfC..

20. **COMMENT:** The panel commented that a large number of studies are cited in Section 4.2.2.2. Effects on Stem Populations, with little discussion of their relationship to each other or to the process of benzene-induced bone marrow disease, some discussion of these issues is warranted.

RESPONSE: The Agency agrees and has rewritten this section (Section 4.2.2.2. Effects on Stem Cell Populations) to include a detailed discussion of the evolving development of information dealing with the process of benzene-induced bone marrow disease.

21. **COMMENT:** The panel noted that the study by Exxon (1996) is not included in Section 4.3.1.1. Oral Exposure under Section 4.3.1. Reproductive Toxicity. It is referenced but not discussed in the draft.

RESPONSE: The study is discussed in Section 4.3.2.1. Oral Exposure under Section 4.3.2. Developmental Toxicity since it is a developmental toxicity study rather than a reproductive toxicity study.

22. **COMMENT:** The panel indicated that the Agency did not justify its conclusions regarding the Kuna and Kapp (1981) study. The conclusions were that exposure to benzene at 50 ppm produced fetotoxicity in rats and this number was a LOAEL. Furthermore, it was also concluded by the Agency that benzene produced skeletal variants and should be considered to be teratogenic at 500 ppm.

RESPONSE: The Agency concluded that because benzene produces fetotoxicity in rats at 50 ppm based upon the evidence from this study and, at the same time, produces no significant adverse effects at 10 ppm from the Kuna and Kapp et al (1981) study, this should be considered a LOAEL That benzene manifests a teratogenic potential at 500 ppm are conclusions of Kuna and Kapp. However, in summary, 13 litters and 142 fetuses were examined from a group of Sprague-Dawley rats exposed to 500 ppm; 30 fetuses from six litters had delayed ossification ($p<0.05$) and four fetuses from 4 litters had skeleta variants and abnormalities. In the group exposed to 50 ppm, 125 fetuses from 15 litters were examined; 23 fetuses from six litters had variants ($p<0.05$). No such observations were made at 10 ppm. The authors of the study concluded that the effects observed were benzene-induced at concentrations of 50 and 500 ppm. The authors of the study also observed that at 500 ppm, the abnormalities were exencephaly, angulated ribs, ossification of the forefeet out of sequence, delayed ossification in the skull, vertibral column, rib cage, pelvic girdle and extremities and significantly fewer tail bones. Based upon this evidence Kuna and Kapp, not the Agency, concluded that benzene appeared to be "teratogenic" at 500 ppm. No abnormalities were observed at 10 ppm. A LOAEL of 50 ppm and a NOAEL of 10 ppm appears to be supported by the experimental evidence. It does seem likely that Kuna and Kapp are correct. See section 4.3.2.2. for a detailed discussion of this paper.

23. **COMMENT:** As noted in Section 4.1.2. several relevant occupational studies, were omitted from the document (e.g. Collins et al. [1991], Fishbeck et al. [1978], Townsend et al [1978] and Yardley-Jones et al [1988]).

RESPONSE: These studies were not excluded from the document except for Yardley-Jones et al (1988). All the studies pointed out by the Panel are discussed in section 4.1 Studies in Humans and are summarized in table 4.1.

24. **COMMENT:** For the RfD calculated from the human data, it is unlikely that a UF for extrapolation from a LOAEL to a NOAEL will be needed in light of the human studies that identified a NOAEL.

RESPONSE: The Agency feels that the human studies with the exception of Rothman et al (1996a) have serious shortcomings including Tsai et al (1983) that preclude their use in the development of an RfD. The Agency will continue to use an UF of 10 for extrapolation from LOAEL to a NOAEL because the levels at which there appears to be no adverse effects, such as in the Tsai et al (1983) study, are unstable because of inherent deficiencies in the data. The study is basically one consisting only of current employees who are still working and hence are a survivor population. The sick or deceased members of this cohort are not represented because of their absence. Furthermore, this group of medically surveyed employees are healthy and young. They have been exposed to minimal levels of benzene for a short time that generally do not exceed 0.53 ppm and probably are a lot less based upon survey results. They perhaps are not much different from background.

25. **COMMENT:** If a review of the omitted occupational data identifies a NOAEL from a chronic occupational study that is appropriate as the basis for the RfD and RfC, the composite UF would be 30 (10 for intrahuman variability and 3 for lack of a 2-generation study) for both the RfD and RfC.

RESPONSE: As mentioned in the response to comment no.2, the Agency justified the use of the Rothman et al (1996a) study as the principal human study for the calculation of the RfD and RfC. However, the Agency has selected a different LOAEL from that study and has chosen the following UFs: a factor of 10 for potentially sensitive human subpopulations, 10 for the use of a LOAEL, 3 for database deficiencies for a final UF of 300. For the RfD based upon the NTP (1986) study, the Agency used the following UFs: 10 for interspecies extrapolation, 10 for intraspecies extrapolation, 10 for LOAEL to NOAEL conversion and 3 for database deficiencies for a combined UF of 3000. The Ward et al (1985) study provided the co-principal study for support of the RfC. A NOAEL was used here which meant that the composite uncertainty factor could be reduced by 10 because of the use of a NOAEL.

For the RfC using the $BMCL_{[ADJ]}$ value of 8.2 mg/m^3, several UFs were applied. Since the benchmark concentration is considered to be an adverse effect, an effect level extrapolation factor analogous to the LOAEL-to-NOAEL a UF of 3 is used. A factor of 10 was used for intraspecies differences in human response as a means of protecting sensitive human subpopulations. And UF of 3 was chosen to account for database deficiencies. An overall UF of 3 X 10 X 3 = 100 was used to calculate the chronic inhalation RfC based upon benchmark analysis. For the RfD, again because the benchmark concentration is considered to be an adverse effect, an LOAEL-to-NOAEL UF of 3 was used in the analysis. A factor of 10 was used for intraspecies differences in human response. And finally, a UF of 3 was chosen to account for database deficiencies due to the lack of a two-generational reproductive/ developmental toxicity study for benzene. An overall UF of 3 X 10 X 3 = 100 was used to calculate the chronic oral RfD. See sections 5.1.1., 5.1.2. and 5.1.3. for discusion of the derivation of the RfD, its Ufs and corresponding benchmark dose analysis. See sections 5.2.1., 5.2.2. for a discussion of the

derivation of the RfC, its Ufs and the corresponding benchmark dose analysis. The dose-response summary will be found in section 5.3

PUBLIC COMMENTS

American Petroleum Institute

The American Petroleum Institute (API) submitted comments on the Toxicological Review of Benzene document. API presented their comments in three sections: API analysis, hematological review and comments prepared by Myerson Occupational and Environmental Medicine and a commentary on critical study prepared by Howard M. Kippen on behalf of the API. API's major technical concerns were classified into three sections; the selection of biological endpoints, the particular choice of key studies, and the application of uncertainty factors in calculation of benzene risk. The specific concerns and responses are as follows:

1. **Disregard for Limitations of Epidemiological Method:**

COMMENT: API claims that the report cites several old case reports as supporting information for assessment of non-cancer endpoints and does not discuss the well known information on conclusions that can be drawn from such sources. API cites a study of Kahn and Muzyka as an example of a case study being useless for determining the impact of low-level benzene exposure and several other studies on reproductive and developmental effects.

RESPONSE: The Agency agrees with the overall observations of the API. Kahn and Muzyka study has been deleted in the revised draft document. It is the intent and practice of the Agency to describe and evaluate all relevant available published data including case studies irrespective of their limitations. The specific observations of API about certain case studies have been noted and incorporated in the revised document.

2. **Insufficient Considerations of PBPK Models:**

COMMENT: The API suggested that PBPK models should be used in certain aspects of non-cancer assessment such as for dose and inter- and intraspecies extrapolation.

RESPONSE: The Agency agrees with the suggestion of the API regarding the use of PBPK models, however, the current PBPK models are insufficiently refined to allow their use to predict human metabolism and dosimetry of benzene. The key areas of refinements needs to include the kinetics and putative toxic metabolites of benzene such as hydroquinone, benzoquinone, muconaldehyde, and benzene oxide. However, descriptions of their role in target organ toxicity and kinetics to be useful in improving uncertainties in non-cancer risk assessment are lacking. The Agency reviewed all the published PBPK toxicokinetic data on benzene as described in the Section 3.5 and it supports the conclusions as outlined in document based on the current scientific consensus on the issue. The External Peer-Review Panel also agreed with the EPA's conclusions

3. **Selection of Critical Effect:**

COMMENT: The API stated that the case has not been made in the report that immunotoxicity is an effect caused by benzene exposure and the most sensitive effects are hematologic and not immunotoxic, in nature.

RESPONSE: The Agency agrees with the API's general comments. However, the Agency disagrees that immunotoxicity is not an endpoint of concern for benzene toxicity. As discussed in Section 4.4.2 Immunotoxicity, dose-related adverse effects of spleen weight and cellularity and various measures of immune function have been observed in experimental animals following both oral and inhalation exposure to benzene. The Agency reconsidered Hsieh et al (1988b) study for derivation of an RfD, however, it is rejected based on careful review of the data and several short-comings of the experimental protocol as described in section 5.1 of the revised document.

4. **Selection of Critical Study:**

COMMENT: The API noted that the two studies chosen by the Agency for derivation of RfC/RfD estimates be investigated further and several other studies might be useful for analysis and comparison.

RESPONSE: In the revised document, the Agency has re-evaluated all the relevant studies and considered a weight-of-the-evidence approach for analyzing the risk of hematological effects from benzene exposure. The Agency selected three studies (Rothman et al, 1996a; Ward et al., 1985; and NTP, 1986) as the critical studies for derivation of RfC/RfD for benzene based on hematotological hematotoxicity effects.

5. **Review of Rothman et al., 1996a:**

COMMENT: The API pointed out several strengths and weaknesses of the Rothman et al., 1996a study. Furthermore, the API suggested a more rigorous analysis of the dose-response of peripheral blood parameters of benzene exposure groups as a part of an overall weight-of-the-evidence analysis of the hematotoxicity risk due to benzene.

RESPONSE: The Agency agrees with the API comments. The revised document responds to the API's concerns. Additional details for all relevant studies have been included. The Agency further analyzed and interpreted two additional studies; the Ward et al, 1985 study and the NTP, 1986 study and reanalysed Rothman et al 1996a to provide a benchmark dose analysis as a part of the overall weight-of-the-evidence analysis of the hematotoxicity risk due to benzene.

6. **Uncertainty Factors/RfC and RfD Determination:**

COMMENT: The API recommends that the Rothman et al., 1996 study should not be used as the key study for the noncancer assessment of benzene and commented on the use of uncertainty factors. The API proposed that in the event that weight-of-the-evidence is not adopted, the "<31" ppm exposure group from the Rothman et al., 1996 study is a more appropriate starting point for the critical effect and for the derivation of a RfC for benzene based on the LOAEL in the range of 10-20 ppm along with the other literature. Uncertainty factors of 3 - 5 for LOAEL to NOAEL extrapolation, 3 - 10 for intraspecies variation, and a small residual uncertainty regarding the subchronic to chronic dose extrapolation resulting in approximately 10 - 50 fold uncertainty factor was suggested. API further suggested that if the animal effects are used as the basis, perhaps another uncertainly factor of 3 - 10 might be also used for interspecies variability.

RESPONSE: The Agency disagrees with the API's overall recommendations not to use the Rothman et al., 1996a study and furthermore finds the comments on the use of uncertainty factors are not justifiable based on the overall weight-of-the-evidence reanalysis and

interpretation of the Rothman et al., 1996a study; Ward et al., 1985 study and the NTP, 1986 study as well as benchmark dose calculations for these studies. With respect to the uncertainty factors that are used based upon the LOAEL and upon the $BMCL_{[adj]}$ for the RfC and RfD, refer to the response to comment # 27 of the External Peer Review Panel. Also, please see response under comment #2 of the External Peer Review Panel

Consultants in Toxicology, Risk Assessment and Product Safety (CTRAPS)

COMMENT: The CTRAPS addressed three topics related to the document, i.e. 1) the nature of the peer-review meeting, 2) the scientific quality of the draft toxicological review and 3) the relationship of the draft toxicological review to a previous document about benzene.

In summary, the CTRAPS recommended that EPA should withdraw both Carcinogenic Effects of Benzene: An Update (EPA/600/P-97/001F; April, 1998) and the Draft Toxicological Review of Benzene (Noncancer Effects)(NCEA-S-0455, September, 1998), integrate the two documents, reinterpret the quantitative regulatory standards for the health effects of benzene, and obtain a legitimate scientific peer-review of the integrated document by an advisory group in compliance with Federal Advisory Committee Act (FACA).

RESPONSE: The Agency followed the established science Peer-Review Policy Guidance (U.S. Environmental Protection Agency, 1998. Science Policy Council Handbook: peer review, EPA 100-B-98-001. Science Policy Council. Washington, DC) and the process in conducting external expert peer-panel and public review of the documents identified by the CTRAPS. The Agency believes no violation of the FACA occurred since the peer-panel review meetings did not fall under the FACA regulations as alleged by the CTRAPS. The District Court for the District of Columbia denied CTRAPS's cross-motion for partial summary judgement and granted EPA's motion for summary judgement. Furthermore, CTRAPS's notice of appeal filed on May 27, 1998, was denied in the appellate court of the District of Columbia on April 30, 1999. The allegation of CTRAPS' contention that "the EPA contractor, the American Institute of Biological Sciences, held a second, closed meeting of the advisory committee without allowing public access" has no standing. The Agency published Federal Registry Notice (U.S. Environmental Protection Agency (1998). Draft toxicological review of benzene (noncancer effects): in support of summary information on the Integrated Risk Information System. Federal Register 63(193): 53654-53655.) announcing the public meetings provided opportunities for both oral and written comments. In fact, the CTRAPS's representative attended both the public meetings and provided written comments during public comment periods. Therefore, the CTRAPS allegation is baseless and misleading. The Agency did not hold these peer-panel review meetings. They were held by independent contractors supported by EPA and open to the public. The external peer-review panel members were selected by the contractors. The Agency considered comments of the peer-review panel as well as those of the public and revised the document. The CTRAPS argued that the document does not make appropriate choices among the studies available for dose-response assessment of benzene ingestion or inhalation. The Agency disagrees with the general statement, however, a revised document addresses specific concerns of the peer-review panel as well as the public comments (see earlier responses). The CTRAPS observed that the nonlinear dose-response relationship between benzene exposure and the risk of acute myelocytic leukemia is supported by the mode of action information and by empirical data. The Agency believes that the CTRAPS's argument is not currently supported by a critical evaluation of the benzene toxicity information and the Agency's position is supported

by the scientific community at large. (Krewski et al., 2000. J. Tox. Environ. Health, Part A, 61: 307-338) and an External Peer-Review Panel Report that was prepared shortly after the peer-panel review meeting. Furthermore, the comment is not related to the document in question, therefore, it is irrelevant.